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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/715,983	11/20/2000	Brett P. Monia	ISPH-0519	6803

7590 11/19/2002

Kathleen A. Tyrrell
Licata & Tyrrell P.C.
66 E. Main Street
Marlton, NJ 08053

EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	9

DATE MAILED: 11/19/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary

Application No.	Applicant(s)
09/715,983	Monia et al
Examiner	**Art Unit**
Jane Zara	1635

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) X Responsive to communication(s) filed on *Sep 20, 2002*.

2a) ☐ This action is **FINAL**. 2b) X This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) X Claim(s) *1, 2, and 4-63* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) X Claim(s) *1, 2, and 4-63* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) X Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) X	Notice of References Cited PTO-892	4	Interview Summary PTO-413 Paper No s.
2) ☐	Notice of Draftsperson's Patent Drawing Review PTO-948	5	Notice of Informal Patent Application PTO-152
3) X	Information Disclosure Statement s PTO-1449 Paper No s 4	6	Other:

DETAILED ACTION

Claims 1, 2, 4-63 are pending in the instant application.

Election/Restriction

The amendment filed September 20, 2002, in response to the restriction requirement mailed August 21, 2002, is acknowledged. Applicant timely traversed the restriction (election) requirement in Paper No. 8.

Applicant's election of SEQ ID NO: 1 with traverse in Paper No. 8 is acknowledged. The traversal is on the ground(s) that the search of the individual sequences claimed would not constitute a burden because all of the individual sequences represent antisense (sub)sequences of a parent target molecule. This is not found persuasive because a search of appropriate databases required to search all of the individual sequences is a burden to the examiner and the searching facilities. Furthermore, each antisense sequence obtained from a larger target nucleic acid molecule embodies a separate, patentable invention and therefore the restriction requirement is proper.

The requirement is still deemed proper and is therefore made FINAL.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or

improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 2, 4-14, 23 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-19 of U.S. Patent No. 6,100,090. Although the conflicting claims are not identical, they are not patentably distinct from each other because the pending claims of the instant application are drawn to compositions comprising antisense oligonucleotides between 8-30 nucleobases which specifically target and inhibit the expression of PI3K p85, and which oligonucleotides optionally further comprise phosphorothioate internucleotide linkages, 2'-O-methoxyethyl sugar moieties, 5-methyl cytosine nucleobases, or chimeric oligonucleotides, and which compositions further comprise a

pharmaceutically acceptable carrier and a colloidal dispersion system, and the claims of USPN 6,100,090 are drawn to compositions comprising antisense oligonucleotides between 8-30 nucleobases which specifically target and inhibit the expression of PI3K p85, including specific antisense oligonucleotide sequences, and which oligonucleotides optionally further comprise phosphorothioate internucleotide linkages, 2'-O-methoxyethyl sugar moieties, 5-methyl cytosine nucleobases, or chimeric oligonucleotides, and which compositions further comprise a pharmaceutically acceptable carrier and a colloidal dispersion system.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 48 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 48, line 2, the term "preferentially inhibits" is vague and unclear.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23, 49-57 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to antisense oligonucleotides between 8-30 nucleobases which specifically target and inhibit the expression of the nucleic acid encoding a truncated form of human PI3K p85 of SEQ ID NO: 1, or which antisense oligonucleotides target a region of PI3K p85a which is not found in PI3K p50a, or not found in PI3K p55a, or which inhibit the expression of all splice variants encoded by PI3K p85a, or which alter the ratio of PI3K p85a to PI3K p50a or to PI3K p55a expressed by a cell or tissue. The specification and claims do not adequately describe the essential elements of the claimed invention. No adequate description has been provided for the genus drawn to truncated forms of human PI3K p85, nor to the splice variants encoded by PI3K p85, nor the target regions of PI3K p85a which are not found in PI3K p50a or in p55a, nor what defines an alteration of the ratio of PI3K p85a to p50a or p55a. Furthermore, the claims read on numerous structural variants and the general knowledge and level of skill in the art do not supplement the omitted description because specific, not general guidance is what is needed. Since the genus is highly variant, and the description provided is insufficient, one of skill in the art would reasonably conclude that the disclosure and/or claims fail to provide either an adequate description of a representative number of species to describe the broad genus claimed. Thus, applicant was not in possession of the claimed genus.

Claims 15-63 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions and methods for inhibiting the expression of human PI3K p85a of SEQ ID NO: 1 in vitro, comprising the administration of antisense oligonucleotides 8-30 oligonucleotides in length which specifically target human PI3K p85a, does not reasonably provide enablement for antisense oligonucleotides between 8-30 nucleobases which specifically target and inhibit the expression of the nucleic acid encoding a truncated form of human PI3K p85 of SEQ ID NO: 1, or which antisense oligonucleotides target a region of PI3K p85a which is not found in PI3K p50a, or not found in PI3K p55a, or which inhibit the expression of all splice variants encoded by PI3K p85a, or which alter the ratio of PI3K p85a to PI3K p50a or to PI3K p55a expressed by a cell or tissue, or the ability to treat or prevent any disease or condition associated with PI3K p85a expression in an organism, or to modulate signal transduction in an organism comprising the administration of these antisense oligonucleotides. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to antisense oligonucleotides between 8-30 nucleobases which specifically target and inhibit the expression of the nucleic acid encoding a truncated form of human PI3K p85 of SEQ ID NO: 1, or which antisense oligonucleotides target a region of PI3K p85a which is not found in PI3K p50a, or not found in PI3K p55a, or which inhibit the expression of all splice variants encoded by PI3K p85a, or which alter the ratio of PI3K p85a to

PI3K p50a or to PI3K p55a expressed by a cell or tissue, or the ability to treat or prevent any disease or condition associated with PI3K p85a expression in an organism, or to modulate signal transduction in an organism comprising the administration of these antisense oligonucleotides.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of antisense treatment in organisms. Branch and Crooke teach that the in vivo (whole organism) application of nucleic acids (such as antisense) is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of *in vivo* inhibition of target genes. (See entire text for Branch and especially pages 34-36 for Crooke). The high level of unpredictability regarding the prediction of antisense efficacy in treating disease states was illustrated in the clinical trial results obtained by ISIS pharmaceuticals for the treatment of Crohn's disease using antisense targeting ICAM-1, whereby the placebo treatment was found more successful than antisense treatment (BioWorld Today: See entire article, especially paragraphs 3 and 5-7 on page 1). Additionally, Palu et al teach that the success of gene delivery using virally derived vectors is dependent on the empirical determination of successful gene transduction for a given vector and a given target cell (See entire article, especially page 4, section 2.)

Tamm et al. in a review article discussing the therapeutic potential of antisense in treating various forms of neoplasia, conclude that "Proof of clinical efficacy, of any of the antisense oligonucleotides in the field of oncology, is still missing." (see especially pages 490-493 for a summary of various clinical trials in process using antisense). Additionally, Agrawal et al point to various factors contributing to the unpredictability of antisense therapy, including non-antisense effects attributed to secondary structure and charge, as well as biological effects exerted by sequence motifs existing within the antisense sequences, all providing for unpredictable in vivo side effects and limited efficacy (e.g. see pages 72-76). Agrawal et al speak to the unpredictable nature of the antisense field thus: "It is therefore appropriate to study each antisense oligonucleotide in its own context, and relevant cell line, without generalizing the results for every oligonucleotide." (see page 80). Cellular uptake of antisense oligonucleotides by appropriate target cells is another rate limiting step that has yet to be overcome in achieving predictable clinical efficacy using antisense. Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of antisense oligonucleotides in vitro and in vivo (see Agrawal et al especially at pages 79-80; see Chirila et al in its entirety, especially pages 326-327 for a general review of the "important and inordinately difficult challenge" of the delivery of therapeutic antisense oligonucleotides to target cells).

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of inhibiting any and or all truncated forms of human PI3K p85 of

SEQ ID NO: 1, or inhibiting the expression of any and/or all splice variants encoded by PI3K p85a, or altering the ratio of PI3K p85a to PI3K p50a or to PI3K p55a expressed by a cell or tissue in vitro or in vivo, or treating or preventing any and/or all diseases or conditions associated with PI3K p85a expression in an organism, or modulating signal transduction in any organism comprising the administration of antisense oligonucleotides.

The specification teaches the inhibition of human (SEQ ID NO: 1) and mouse PI3K p85 in vitro comprising the administration of antisense oligonucleotides 8-30 nucleobases in length, the inhibition of PI3K p85 and the splice variant PI3K p85-alpha, as well as a reduction in blood glucose and serum insulin levels in mice following the administration of antisense ISIS 131410. The specification fails to teach the modulation of signal transduction in any organism, or the treatment or prevention of any and/or all diseases or conditions associated with PI3K p85 expression in an organism, comprising the administration of antisense between 8-30 nucleobases which specifically target PI3K p85. One skilled in the art would not accept on its face the examples given in the specification as being correlative or representative of the successful modulation of signal transduction in an organism, or the successful prevention or treatment of any and/or all diseases or conditions in an organism which are associated with PI3K p85 expression comprising the administration of antisense, in view of the lack of guidance in the specification and known unpredictability associated with predetermining the efficacy of antisense in treating an organism for any and/or all diseases or conditions associated with a target molecule comprising the administration of antisense. The specification as filed fails to provide any

particular guidance which resolves the known unpredictability in the art associated with in vivo delivery, prevention or treatment effects provided for any disease or condition associated with a particular target molecule by antisense administered, and specifically regarding expression of nucleic acids encoding any truncated form of human PI3K p85 of SEQ ID NO: 1, or which antisense oligonucleotides target a region of PI3K p85a which is not found in PI3K p50a, or not found in PI3K p55a, or which inhibit the expression of all splice variants encoded by PI3K p85a, or which alter the ratio of PI3K p85a to PI3K p50a or to PI3K p55a expressed by a cell or tissue.

The breadth of the claims and the quantity of experimentation required. The breadth of the claims is very broad. The claims are drawn to antisense oligonucleotides between 8-30 nucleobases which specifically target and inhibit the expression of the nucleic acid encoding a truncated form of human PI3K p85 of SEQ ID NO: 1, or which antisense oligonucleotides target a region of PI3K p85a which is not found in PI3K p50a, or not found in PI3K p55a, or which inhibit the expression of all splice variants encoded by PI3K p85a, or which alter the ratio of PI3K p85a to PI3K p50a or to PI3K p55a expressed by a cell or tissue, or the ability to treat or prevent any disease or condition associated with PI3K p85a expression in an organism, or to modulate signal transduction in an organism comprising the administration of antisense oligonucleotides. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, modes of delivery and formulations to target appropriate cells and or tissues harboring the wild type and any and/or all truncations or splice variants of PI3K p85 in vitro or in vivo whereby the target nucleic acid is

inhibited in vivo, and further that treatment or preventive effects are provided for any and/or all conditions or diseases associated with PI3K p85 expression. Since the specification fails to provide any particular guidance for the inhibition of all truncated or alternately spliced variants of PI3K p85 in vitro or in vivo, or for the prevention and/or treatment of any and/or all diseases or conditions associated with PI3K p85 expression comprising the administration of antisense, and since determination of the factors required such in vivo success is highly unpredictable, it would require undue experimentation to practice the invention over the broad scope claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 12-15 are rejected under 35 U.S.C. 102(b) as being anticipated by either Zauli et al or Skorski et al.

Zauli et al (IDS document "AH") teach compositions comprising antisense oligonucleotide compounds between 8-30 nucleobases which specifically target and inhibit the expression of human PI3K p85 of SEQ ID NO: 1 in vitro, and which compositions further

comprise a pharmaceutically acceptable diluent and a colloidal dispersion system (See especially the abstract on p 883, first and fourth-sixth full paragraphs on page 884 and figure 7 on p 891).

Skorski et al (IDS document "AF) teach compositions comprising antisense oligonucleotide compounds between 8-30 nucleobases which specifically target and inhibit the expression of human PI3K p85 of SEQ ID NO: 1 in vitro, and which compositions further comprise a pharmaceutically acceptable diluent and a colloidal dispersion system (See especially the abstract on p 726, paragraphs 3, 5 and 6 on p 727, and figures 3 and 4 on pp 729 and 730 respectively).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 4-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zauli and Skorsky as applied to claims 1, 2 and 12-14 above, and further in view of Schlessinger et al, the combination in view of Milner et al and Baracchini et al.

The claims are drawn to compositions comprising antisense oligonucleotide compounds between 8-30 nucleotides which specifically target and inhibit the expression of human PI3K p85

of SEQ ID NO: 1 in vitro, and which oligonucleotides further comprise a phosphorothioate internucleotide linkage modification, a 2'-O-methoxyethyl sugar modification, a 5-methyl cytosine nucleobase modification, and may optionally comprise a chimeric oligonucleotide, and which compositions further comprise a pharmaceutically acceptable diluent and a colloidal dispersion system.

Zauli and Skorski are relied upon as cited in the 102 rejection above.

These primary references do not teach antisense which target other portions of human PI3K p85 sequence, nor any internucleotide, nucleobase or sugar modifications, nor chimeric oligonucleotides.

Schlessinger et al teach the polynucleotide sequence encoding human PI3K p85 of SEQ ID NO: 3 (See especially claim 21, figure 4 and the accompanying sequence alignment data).

Milner teaches methods of designing and assessing the ability of various antisense oligonucleotides to target and inhibit the expression of a target nucleic acid of known nucleic acid sequence in vitro (See entire document, especially figure 1 on p 538).

Baracchini et al teach the incorporation of phosphorothioate internucleotide linkages, 2'-O-methoxy ethyl sugar modifications, 5 methyl cytosines and chimeric structures into antisense oligonucleotides for enhancing target binding, cellular uptake and stability of antisense oligonucleotides (see col. 5-9).

It would have been obvious to one of ordinary skill in the art to target and inhibit the expression of human PI3K p85 in vitro comprising the administration of antisense

oligonucleotides between 8-30 nucleobases because the in vitro targeting and inhibition of human PI3K p85 using antisense between 8-30 nucleobases had been taught previously by either Skorsky or Zauli. Furthermore, Schlessinger teaches the polynucleotide sequence of the target nucleic acid encoding human PI3K p85 of SEQ ID NO: 1 and Milner teaches methods of designing and assessing antisense oligonucleotides for their ability to target and inhibit the expression of a known target gene in vitro. One of ordinary skill in the art would have been motivated to utilize such a method of finding optimal antisense oligonucleotides between 8-30 nucleobases which best target and inhibit PI3K p85 expression in order to study this target molecule's role in various cellular processes, such as cellular hematopoiesis, cellular proliferation and cellular attachment, as taught previously by Skorski and Zauli. One of ordinary skill in the art would have been motivated to incorporate various modifications into antisense such as internucleotide linkage, nucleobase, or sugar modifications, as well as designing chimeric antisense oligonucleotides, because Baracchini had taught previously that such modifications contribute to the stability, cellular uptake and target binding of antisense oligonucleotide compounds. One of ordinary skill in the art therefore would have expected that antisense comprising such modifications would exhibit enhanced stability, cellular uptake and target binding. Therefore, the invention has a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(703) 306-5820.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (703) 305-3413. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JZ

November 7, 2002